Cystic fibrosis: Nutritional consequences and management

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Life expectancy for patients with Cystic Fibrosis (CF) has steadily improved during the last three decades, and death in childhood is now uncommon. Nutrition is a critical component of the management of CF, and nutritional status is directly associated with both pulmonary status and survival. Expert dietetic care is necessary, and attention must be given to ensuring an adequate energy intake in the face of demands which may be increased by inadequately controlled malabsorption, chronic broncho-pulmonary colonisation by bacteria and fungi, exacerbations of acute lung infection, impaired lung function, and the need for rehabilitation, repair and growth.

Pancreatic enzyme replacement therapy (PERT) is needed by up to 90% of CF patients in Northern Europe, where the ‘severe’ mutation ΔF508 predominates, but a smaller proportion in Mediterranean countries and elsewhere, because pancreatic insufficiency is one of few features of CF which correlate with genotype.

Complications of CF including liver disease and CF-related diabetes pose further challenges. In addition, deficiency of specific nutrients including fat soluble vitamins (particularly A, E and K) essential fatty acids and occasionally minerals occur for a variety of reasons. Osteopenia is common and poorly understood. Liver disease increases the likelihood of vitamin D deficiency. Glucose intolerance and diabetes affect at least 25% of CF adults, and the diabetes differs from both types 1 and 2 diabetes mellitus, but it inversely correlates with prognosis.

Management consists of anticipating problems and addressing them vigorously as soon as they appear. Supplements of vitamins are routinely given. Energy supplements can be oral,
enteral or, rarely, parenteral. All supplements, including PERT, are adjusted to individual needs.

**Key words:** pancreatic insufficiency (PI); pancreatic sufficiency (PS); pancreatic replacement therapy (PERT); energy balance; vitamins; essential fatty acids; liver disease; diabetes; osteopenia.

Cystic Fibrosis (CF) is a serious, chronic genetic disease affecting the lungs and digestion in children, but it is no longer often fatal at that age. Most children grow up with the disorder, and adult physicians, particularly pulmonologists, inherit the accumulated effects of CF on lung function and nutrition, which may be further affected by such complications as liver disease and diabetes.

A direct effect of nutritional growth retardation in CF on lung growth has been demonstrated. The central role of nutrition during childhood was highlighted by Mahadeva and colleagues, who noted that it was the most important single factor determining pulmonary status (and hence likely survival) in CF adults. This supported the earlier observations of Corey et al, who reported that the major factor accounting for longer survival in Toronto than in Boston was the greater emphasis on maintenance of normal growth rates and nutritional status in the former. This correlation between nutritional status and survival continues in adult life, and becomes particularly apparent when end-stage respiratory failure is accompanied by cachexia. The degree of wasting is a good predictor of mortality independent of lung function and levels of oxygen and carbon dioxide. The aim of the physician and dietitian caring for CF patients is to keep children growing at a normal velocity, and to maintain or improve nutritional status (BMI) in adults, often in the face of increasing respiratory disease. They must also ensure adequate intake of vitamins (particularly A, E and K), minerals, and perhaps other nutrients such as essential fatty acids whose importance is still being investigated. Complications such as diabetes and cirrhosis may present further difficulties. Guidelines for the nutritional management of CF have been produced both in Europe and North America.

**PATHOPHYSIOLOGY OF NUTRITIONAL DEFICITS**

Cross-sectional data from the UK Cystic Fibrosis register showed that the mean height and weight standard deviation (Z) scores of both male and female CF children were significantly below those of the general population during the first decade of life, after which there was a progressive decline in both parameters. Body Mass Index (BMI), was however maintained around normal in young children, indicating that they were small but not wasted, but again it became progressively lower with age, particularly in males. Similar data were provided by the (US) Cystic Fibrosis Foundation. Age at diagnosis has an influence: infants diagnosed by neonatal screening have a better nutritional status at the age of 10 years than those diagnosed because of clinical symptoms. Pubertal delay, seen even in well-nourished patients, may explain some of the early growth decline, but the most important cause is probably the onset of increasingly severe chronic lung disease.

**Pancreatic insufficiency** (PI), which is present in 85–90% of patients in Western European populations, is a major reason for failure to thrive in infancy, particularly before the diagnosis of CF is made, when up to 80% of fat may be recovered in stools because of lipase deficiency. When adequate treatment is given, catch-up growth may
take two years before the child reaches his or her subsequent growth trajectory. If pancreatic enzyme replacement therapy (PERT) is inadequate, it may also strongly contribute to malnutrition in the CF adult. Some CF patients who are initially pancreatic-sufficient (PS) later become PI as the pancreas undergoes progressive damage, and it is wise to check the PS individuals from time to time, most conveniently using the fecal elastase test,\textsuperscript{11,63,64} to see whether this has happened. Recent work has shown that the apparently excessive production of enzymes by the healthy pancreas may not in fact be profligate, but may be necessary for normal digestion of certain substrates.\textsuperscript{12} However, care must be taken to avoid overdosage of enzymes, which can result in thickened fibrous strictures of the colon and terminal ileum (fibrosing colonopathy), particularly in children.\textsuperscript{44} Furthermore, exceeding the recommended upper limit of enzyme dosage (10 000 lipase units/kilo/day) does not improve fat absorption, and if significant steatorrhoea persists at that level the use of an adjunct such as omeprazole or misoprostol should be considered.\textsuperscript{13}

Rapid weight loss and/or decline in pulmonary function unexplained by exacerbation of respiratory infection may indicate the onset of diabetes mellitus, which affects up to a third of adult patients over the age of 25 years in a Danish population.\textsuperscript{14} A large US CF centre found a diabetes prevalence of 9, 26, 35 and 43% in patients aged 5–9, 10–19, 20–30 and >30 years respectively.\textsuperscript{51} Cystic fibrosis-related diabetes (CFRD) is typically not accompanied by ketosis, and also differs in other respects from both type 1 and type 2 diabetes.\textsuperscript{15} Although it was formerly believed that diabetic complications were unlikely to emerge during the expected life span of the CF patient, this is no longer a tenable position and CFRD patients must be treated with the same attention to blood sugar control as other diabetics. Indeed, CFRD is not only associated with worse nutritional status and pulmonary disease but also with a six-fold greater mortality rate. The diagnostic criteria for CFRD have been published in a recent consensus report of the US CF Foundation. They are: (1) 2-hour plasma glucose (PG) >11 mmol/l during a 75 g oral glucose tolerance test, (2) fasting PG >7.00 mmol/l on two or more occasions, (3) fasting PG >7.0 mmol/l plus casual PG >11.1 mmol regardless of time of last meal, and (4) casual PG >11.1 mmol/l on two or more occasions with symptoms. Presentation is usually insidious and not typical of type 1 diabetes even in young people. The HbA1c test is not useful for screening, but can be used for monitoring blood glucose levels when the diagnosis of CF-related diabetes has been established.\textsuperscript{15}

Liver disease. Liver enlargement from hepatic steatosis (fatty liver) is a not uncommon, and usually transient, feature of CF in early childhood, particularly at diagnosis and in case of malnutrition. It is usually attributed to defective hepatic secretion of triacyl glycerols as low density lipoprotein, resulting from diminished apolipoprotein synthesis, and in some cases secondary carnitine deficiency may be a contributory factor.\textsuperscript{30,31} It does not predict later development of biliary cirrhosis, whose genetic and/or environmental causes are unknown but which affects up to 10% of patients.\textsuperscript{32} When cirrhosis does occur it usually begins in the first decade of life and onset of overt clinical features after puberty is rare, i.e. it does not become more common as the CF population ages because of longer survival. Patients with CF and clinically apparent liver disease are likely to have additional nutritional abnormalities, particularly related to fat soluble vitamins, and coagulation defects. Treatment with ursodeoxycholic acid (URSO) should be given as soon as there is any clinical or biochemical evidence of liver disease, but its long term benefits are not yet known. Liver transplantation in CF may be successful (either alone or in combination with lung transplantation) and it has a beneficial effect on nutritional status.\textsuperscript{33}
Various other features of CF may increase the daily energy needs if growth in childhood and body weight and composition in adults are to be maintained. A schematic representation of some of the factors contributing to energy imbalance, and the consequent need for additional calorie intake when it occurs, is given in Figure 1. Resting energy expenditure (REE) accounts for about 60–70% of total energy expenditure, and it is significantly increased (by 7–35%) in patients with CF. It has been claimed that there is no evidence of an underlying abnormality of REE in CF, and it appears to be inversely correlated to lung function and lung parenchyma damage. Others, correcting REE for body cell mass, found that mean REE was significantly increased in CF patients compared with healthy children (119.3 ± 3.1% predicted versus 103.6 ± 5% predicted, p < 0.0001). There was no relation between REE and nutritional or pulmonary disease status in the CF children. However, the raised REE is not always associated with an increase in total energy expenditure (TEE), which is the combined total of REE and activity. Increased REE is likely to be compensated by a decrease of physical activity in CF patients. Chronic inflammation, and acute exacerbations of respiratory infection, also increase REE, which falls again in response to effective antibiotic therapy. Improvement in REE, which is not a routine clinical measurement, is more sensitive than lung function tests and chest radiographs in evaluating patients with CF during acute pulmonary exacerbations.

On the other side of the balance, energy intake is often too low to compensate for the increased losses and demands. Metabolic adjustments (moving the fulcrum) are limited: some fall in REE does occur in conditions of starvation, due to the decrease of fat-free mass, and activity may be consciously or unconsciously reduced. Chronically malnourished children respond by slowing or cessation of linear growth (stunting) but adults cannot downsize. Consequently, wasting (weight loss) occurs, enhanced by pro-inflammatory cytokines such as TNFα, which are released during acute and chronic infection, and which also have anorexic effects. Appetite may also be impaired by cough, respiratory embarrassment, nausea, gastro-oesophageal reflux, abdominal pain, abnormal eating behaviour, depression and the metabolic disturbances of liver disease.

Deficiencies of specific nutrients are well documented in the CF literature. Fat-soluble vitamins are predominantly affected, particularly Vitamins A, E and K. Vitamin D deficiency is not usually important provided that the patient had adequate exposure to

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**Figure 1.** Energy balance in cystic fibrosis. (adapted from Ref. [40]). REE, resting energy expenditure; TEE, total energy expenditure; BMR, basal metabolic rate.
sunlight, except when there is concomitant liver disease. Low levels of each of these are often subclinical, but nonetheless important. Essential fatty acid deficiency may play an important role in the pathophysiology of the disease.

Vitamin A (retinol) deficiency may be unmasked by testing for dark adaptation. Low vitamin A levels are associated with poorer clinical status and impaired lung function. Its precursor, β-carotene, also has antioxidant properties in its own right, and may be an essential supplement for CF patients. Plasma levels of β-carotene are low in practically all pancreatic-insufficient CF patients.

Vitamin E (α-tocopherol) requirements are increased by oxidative stress, which accompanies chronic respiratory infection. Vitamin E levels are frequently low in CF even soon after birth, which may reflect the impaired secretion of the antioxidant glutathione which reaches epithelial surfaces, including those of the lung and the pancreatic duct, through the CFTR channel which is defective in this disease. As a result, free oxygen radicals are not quenched and lipid peroxidation of the long chain polyunsaturated fatty acids in the cell membrane occurs. This probably explains the observation of fatty acid imbalances in some tissues of well nourished infants with CF, as well as in mouse models, and it is noteworthy that the greatest deficiency occurs in the fatty acid with the greatest number of vulnerable double bonds, docosahexaenoic acid (DHA).

Vitamin E deficiency is not corrected by PERT, because bile acids (reduced in CF) are also necessary for β-tocopherol absorption, but it may be improved by concomitant administration of ursodeoxycholic acid. Although overt classical signs of vitamin E deficiency are unusual in adults, it may manifest as a permanent spinal cord demyelinating disease. All patients with CF need vitamin E supplements, regardless of their pancreatic function, and serum levels of vitamins A and E should be regularly monitored.

Vitamin K is not only involved in prothrombin synthesis, but it is also a cofactor in the carboxylation of osteocalcin in bone formation. It is particularly likely to be deficient when liver disease is present. Deficiency of vitamin K is probably an important contributory factor to the osteopenia which is often seen in CF, and which correlates poorly with vitamin D levels.

Iron deficiency, as monitored by serum ferritin levels, is not uncommon. It may be a consequence of poor intake, chronic infection, intestinal or pulmonary bleeding. Exogenous pancreatic enzymes can interfere with iron absorption. Iron is an essential substrate for the growth of Pseudomonas aeruginosa, a major pathogen in CF lungs, and iron supplementation is not routinely indicated.

Zinc levels are often low, and are improved by PERT. Selenium levels may also be low, perhaps related to the previously mentioned disturbance of glutathione secretion, but it is a potentially toxic element and fatalities have resulted from its use in CF. There is no evidence to support routine supplementation.

ESSENTIAL FATTY ACID DEFICIENCY

A deficiency of essential fatty acids (EFA) has been described in CF patients that is characterised by a decrease in plasma levels of linoleic acid (LA) and docosahexaenoic acid (DHA) with an increase in the level of eicosatrienoic acid. EFA deficiency is not due simply to impaired lipid absorption secondary to pancreatic insufficiency, since it
has also been described in patients with normal nutritional status and pancreatic function.\(^{23}\)

Lipid peroxidation of the long chain polyunsaturated fatty acids in the cell membrane may play a role. Alterations in fatty acid metabolism in tissues expressing CFTR have been shown in both CF ‘knock-out’ mice and in CF patients, i.e. an increase in arachidonic acid levels and a decrease in DHA levels.\(^{24}\)

It will be clear that regular supplements of a number of micronutrients are indicated. Some commercial preparations attempt to provide these in a single prescription, a practice which is usually discouraged by drug regulatory authorities. Because of the complexity of CF and the substantial number of components involved, it may be one of the conditions where an exception should be made, but even if multivitamin/combination preparations are used, it is important to monitor blood levels to ensure that the balance of supplements is appropriate for each individual.

**MANAGEMENT**

The interaction of the various factors regulating energy balance is clearly complex, and some CF patients seem to maintain body weight for lengthy periods even though their reported energy intake is apparently less than ‘optimal’, i.e. less than the 120–150% of the recommended daily allowance traditionally advised. However, it is essential to keep all CF patients under close nutritional surveillance, and regular assessment by the dietitian is important. Management must be individualised, and patients vary greatly in their nutritional needs.\(^{42}\) Intervention, when needed, must be prompt and adequate, following the guidelines referred to above.\(^{6,7}\) Table 1 is taken from the categories of nutritional management and intervention for different groups of patients, taken from the 1992 North American consensus report, and still a very useful starting point.\(^{7}\)

The twin objectives of nutritional management are (i) to maintain or improve nutritional status in adults (and growth velocity in children), and (ii) to prevent

<table>
<thead>
<tr>
<th>Category</th>
<th>Target group</th>
<th>Goals</th>
</tr>
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<tbody>
<tr>
<td>Routine management</td>
<td>All CF patients</td>
<td>Nutritional education, dietary counselling, PERT (PI patients) vitamin supplements</td>
</tr>
<tr>
<td>Anticipatory guidance</td>
<td>Patients at risk of energy imbalance; frequent pulmonary infections; periods of rapid growth, but maintaining a weight/height index &gt; 90% ideal weight</td>
<td>Further education to prepare patients for increased energy needs; increased monitoring of dietary intake; increase caloric density of diet as needed; behavioural assessment and counselling</td>
</tr>
<tr>
<td>Supportive intervention</td>
<td>Patients with decreased weight velocity and/or a weight/height index &lt; 90% of ideal weight</td>
<td>All of the above plus oral supplements as needed</td>
</tr>
<tr>
<td>Rehabilitative care</td>
<td>Patients with a weight/height index consistently &lt; 85% of ideal weight</td>
<td>All of the above plus nocturnal enteral supplementation via nasogastric tube or gastrostomy</td>
</tr>
<tr>
<td>Resuscitative and palliative care</td>
<td>Patients with a weight/height index &lt; 75% ideal weight or progressive nutritional failure</td>
<td>All of the above plus continuous enteral feeds or total parenteral nutrition</td>
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nutritional imbalances such as vitamin or mineral deficiencies. There are currently no effective nutritional means of preventing CFRD, and it is too early to know whether URSO can prevent CF-associated cirrhosis.

It is, therefore, axiomatic that CF patients must be regularly reviewed and their nutritional status accurately assessed and recorded. The intervals between basic anthropometric measurements should not be greater than 3 months, and full nutritional assessments—anthropometric, biochemical and perhaps imaging—should be carried out annually (Table 2). Failure to maintain weight, or growth velocity, requires a medical response which may vary from ensuring that any unrecognised or inadequately treated pulmonary infection is dealt with, to employing specifically nutritional approaches including PERT, oral, nasogastric or gastrostomy supplements, and in rare, limited and well-defined situations even parenteral nutrition. Deficiencies of specific micronutrients must also be corrected.

In an update of these recommendations, age-adjusted body mass index percentile (BMI%) has been suggested as a more sensitive indicator of nutritional faltering than weight for height percentile.

Patients with a BMI below the 25th percentile are regarded as at risk, some of whom will need intervention, while those below the 10th percentile are defined as in nutritional failure, when treatment is mandatory.

In many CF clinics the patients are seen by the dietitian at each visit: this is particularly important in the case of newly diagnosed infants and young children, in whom maintenance or improvement of growth velocity is a priority, and when even parents of healthy normal children often need advice on such things as weaning and food refusal. In the case of early diagnosis when the infant is in good condition, such as through neonatal screening, continuation of breast feeding is strongly advised. Human milk has an optimum content of amino acids and essential fatty acids, and also contains lipase and amylase which may compensate for diminished pancreatic secretion. Moreover, the presence of immunoglobulins, lactoferrin, epidermal growth factor and lysozyme in human milk offers protection against infection, and the content of taurine, which is necessary for bile acid synthesis, may enhance fat absorption. Non-breast-fed infants can thrive normally on standard infant formula with adequate pancreatic enzyme therapy, and protein hydrolysate formulas have no advantage over conventional cow’s milk based products.

| Table 2. Routine nutritional assessments at CF clinic visits. |
|---------------------------------|-----------------|----------------|
| **Anthropometric**               | **Dietetic**    | **Laboratory** |
| Height (cm) + centile           | Dietary intake  | Vitamins A, E  |
| Weight (kg) + centile           |                 | Vitamin D      |
| Head circumference in young children (cm) |             | Serum Ca, Fe   |
| BMI                             |                 | Liver function tests |
| Triceps skinfold/mid-arm circumference |                 | Cholesterol, lipids |
|                                |                 | Oral glucose tolerance |
|                                |                 | HbA1c (CFRD only) |
|                                |                 | DEXA scan       |
|                                |                 | 3 day fat balance\(^b\) |

\(^a\) Annually.

\(^b\) At diagnosis and when indicated.
Adults with CF should also be kept under frequent dietetic review, ideally at least 6-monthly, and should have a formal assessment of dietary intake annually. Weight loss should trigger an earlier assessment and appropriate response. Nutritional crisis periods which require particularly close surveillance include the adolescent growth spurt—which may be accompanied by lapses in dietary and medication adherence—and moving out of the parental home, pregnancy, and the onset of CFRD. In most patients, frequently reinforced advice on a suitable high energy, high protein diet is enough to keep them adequately nourished for many years. One danger is that this kind of diet may be deficient in fibre, which is associated with abdominal pain and colonic symptoms, although this is not universally seen and may vary with national dietary customs.

**PANCREATIC ENZYME REPLACEMENT THERAPY (PERT)**

All patients who are pancreatic insufficient (PI), as shown by fat balance studies and/or indirect pancreatic function tests such as faecal elastase or chymotrypsin, should receive pancreatic enzyme supplements. By far the most effective formulations are enteric coated granules or microspheres, which resist inactivation by gastric acid. Even so, because of failure of pancreatic bicarbonate secretion, the pH of the duodenum is often well below the level at which the enzymes—mainly lipase and proteases—are optimally active, and there is considerable evidence that in practice much of the enzyme activity occurs as far down as the terminal ileum, which is not well adapted for absorption of the products of digestion. There are many other physiological and pathological variables which make PERT inefficient, from variation in gastric emptying (both between and within individuals) to variation in the enzyme content of pancreatin preparations between batches and with time in storage. The strength of these products is generally expressed in lipase units, and at the time of manufacture the actual enzyme content can exceed the stated amount by up to 100%, to allow for loss of activity before the expiry date of the batch. It is, therefore, impossible for the patient or physician to know the precise dose of enzyme being taken at any point in time, and in any case the amount needed will depend on the contents of the meal. Balance studies show that while there is a fairly constant ratio between lipase and trypsin content in the PERT product, individuals on treatment vary considerably in their excretion of fat and nitrogen (protein), so that some lose significant amounts of protein but relatively little fat, whereas others excrete much more fat than nitrogen.

Monitoring the effectiveness of the dose is, therefore, not always easy. Patients may tolerate a remarkable degree of steatorrhea without being aware of any abnormality in the stools, but they and their families may comment on the unpleasant odour if there is significant malabsorption of protein. The symptom most often complained of is offensive stools, which is a reflection of excess indoles and skatoles, secondary to poor digestion of protein, not fat, and the poor correlation between fat and nitrogen excretion has already been referred to. More objective than symptoms, regular 3-day fat balances, involving collection of stools, can be performed until a plateau of fat absorption has been reached beyond which no further improvement occurs with escalation of the dose, is a possible but unpopular approach. In practice, provided that the stools are not excessively greasy or offensive, and that the child is growing according to expected centiles or the adult maintaining a steady weight, most clinicians do not usually repeat fat balances after the initial demonstration of pancreatic
insufficiency. Attempts to normalise measured fat balance criteria (better than 90% absorption) can lead to the use of excessive doses of enzymes, which can cause damage to the colon and terminal ileum, leading to thickening and stricture formation which may require more or less extensive surgery. In some cases the patients were taking up to six or even 10 times what we now know to be the upper limit of recommended safe amounts of PERT. Young children are particularly vulnerable to this condition, now known as fibrosing colonopathy, but the incidence has fallen dramatically since the danger was recognised and the use of excessive dosage discontinued. Reported cases were confined to a few countries, mainly the UK and the USA, and the more circumspect prescription of PERT in most other countries seems to have been the reason why it was not seen elsewhere.

As a result of the fibrosing colonopathy experience, consensus reports from both sides of the Atlantic recommended that the maximum daily dose of enzymes should not exceed 10 000 lipase units/kg body weight/day and the starting dose for new patients is usually about a quarter to a third of that upper limit. Many patients need little or no more than the starting dose to achieve satisfactory results, but some continue to have evident malabsorption even when the upper limit is reached, in which case the use of adjunctive treatment with a proton pump inhibitor, a H2 receptor antagonist or misoprostol should be considered. It must be remembered that excess fat excretion does not necessarily signify maldigestion, because absorption of free fatty acids is impaired in CF and no amount of lipase could correct that problem.

Various alternatives to animal pancreas have been proposed as a source of digestive enzymes, including bacterial and fungal lipases. Apart from the fact that they appear to work much less well in patients than in the laboratory, such lipases have the intrinsic problem that they only digest triacylglycerols, whereas human and animal pancreatic secretions contain a variety of other enzymes, each with its unique role in digesting specific substrates present in a normal diet, such as proteases, carboxypeptidase, elastase, colipase, phospholipase, amylases and others. A biologically and economically successful synthetic product incorporating appropriate amounts of lipase and protease may be a mirage, and the long term effects of omitting any of the apparently minor enzymes are not known, so it appears that for the foreseeable future preparations based on hog pancreas are likely to remain the source of PERT.

ORAL SUPPLEMENTS

When nutritional intervention needs to be stepped up (Table 1), there is a wide range of oral supplements from which to choose. Simple energy-dense supplements are the most palatable, and, therefore, encourage adherence, but may prove to be used as food substitutes rather than true supplements, in which case the fact that they tend to be relatively low in protein may be a theoretical disadvantage. Nevertheless, if properly used they can produce a worthwhile degree of weight gain and in some cases they have been so successful that they have replaced gastrostomy feeds in individual patients. However, oral supplements, although much less invasive than enteral or parenteral nutrition, have also been described as unpleasant in taste and there are often difficulties with adherence on a daily basis. Occasionally, the intake of extra energy can expose previously undetected marginal insulin secretion and precipitate CFRD, and this is more likely to occur when the supplemental formula has a high carbohydrate content. The use of growth hormone and other anabolic agents has been recently advocated, since CF is a catabolic condition. Growth hormone improved nutritional status and
clinical condition in a group of prepubertal children who were <10th centile for height and weight despite adequate caloric intake. Megestrol acetate is a progesterone analogue used as an appetite stimulant in cachectic illnesses. Its short-term use in malnourished CF patients resulted in significant weight gain and improved pulmonary function. However, reversible adrenal suppression was observed in most patients. Further study is needed to better define the CF patients who may benefit from the use of anabolic agents.

ENTERAL NUTRITION

If oral supplements, whether simple calorie boosters or more nutritionally complete, fail to correct the problem, the next step is enteral nutrition. If it is anticipated that only a short period of treatment will be needed, for example during recovery from a severe respiratory exacerbation, or from surgery, or before elective surgery, feeds can be given by naso-gastric tube. This is not liked by patients, but even when it is clear that long-term enteral feeding will be needed some will accept or request it as an alternative or preliminary to placement of a gastrostomy. Body image and self-esteem are frequently distorted in CF, especially in cases of underweight, and enteral nutrition is rightly considered by patients and/or parents as a new constraint. Psychological support of the patient may be necessary. Gastro-oesophageal reflux is not a contraindication to enteral nutrition, provided that the efficiency of the antireflux treatment is carefully checked. The decision to use gastrostomy—or nasogastric—feeds, usually given overnight, should not be delayed once it is seriously proposed, because abundant clinical experience has confirmed that the patients who benefit most are those whose nutritional deficits are relatively mild, while conversely the results are usually disappointing when wasting is advanced. The technique of choice is percutaneous endoscopic gastrostomy (PEG), and overnight feeding up to a maximum volume of 1000 ml in adults is generally well tolerated. The aim is to provide about 50% of the daily calorie requirements, and there are numerous suitable preparations available.

Non-elemental formulas, given with PERT, are equally effective as semi-elemental products, and much cheaper. There is no consensus concerning the timing and dosing of pancreatic enzymes, but commonly a rather small dose of enzymes is given by mouth at the beginning of the overnight infusion and a similar dose in the morning. An extra dose may be taken if the patient wakes spontaneously during the night. Fasting blood sugars and percent haemoglobin A1c are usually not predictive of glucose tolerance, making monitoring of capillary glucose necessary during initiation of enteral nutrition. Published short term results are usually very encouraging, particularly when the decision to use this aggressive approach has been made early, but it is less clear whether the initial success is maintained in the long term, particularly if the treatment was not instituted before the FEV1 had fallen to 40% predicted. No study has convincingly demonstrated a beneficial effect of enteral nutrition on the frequency of pulmonary exacerbations.

PARENTERAL NUTRITION

Parenteral nutrition is efficient in improving nutritional status in malnourished CF patients. However, it is a very invasive, complex and expensive treatment, the use of which should be restricted to very few patients with severe malnutrition when enteral
nutrition has failed or is impossible to perform, such as in patients awaiting lung or liver transplantation in a very poor pulmonary and nutritional condition, or in infants with short gut syndrome following neonatal surgery.

Although parenteral nutrition may be beneficial in reversing an acute decline in pulmonary function, it is less likely to affect the chronically compromised lung function characteristic of older patients with CF.

**VITAMINS AND MINERALS**

Guidelines for vitamin and mineral supplementation are available in the European consensus on nutrition in CF patients\(^6\) (Table 3).

**VITAMINS**

Vitamin supplementation should be adjusted as necessary according to blood levels. The serum level of vitamin A is negatively associated with C-reactive protein and other evidence of inflammation, and it is important to distinguish between low serum levels secondary to inflammatory processes and those due to poor nutritional stores.\(^6\) If blood levels of vitamin A remain low despite adequate supplementation, attention should be given to patient compliance and the retinol binding protein and zinc levels should be assessed. Since vitamin A can be responsible for severe birth defects, supplementation should be carefully monitored during pregnancy and should not exceed 10 000 IU/day.

Low bone density is common in CF adults.\(^6\) Bone mass decreases in adolescents and young adults, and as patients live longer the fracture rate is likely to increase as a consequence of normal age-related bone loss. A vitamin D daily dose of between 400 and 2000 IU is usually required to maintain normal vitamin D blood levels. It has been suggested that the serum level of vitamin D should be kept within the upper part of the normal range to ensure optimum bone health.\(^6\) A randomised, double-blind placebo-controlled trial recently showed that twelve months supplementation with 1000 mg calcium and 800 IU vitamin D reduced the rate of bone turnover and bone loss in adult CF patients but these changes did not reach statistical significance. A longer term trial may be necessary.\(^6\) The optimal level of calcium and vitamin D supplementation remains to be elucidated. A prospective and longitudinal study in CF adults (mean age 30.7 years, \(\text{T able 3. Vitamin supplementation in CF (from Ref. [6]).}\)

<table>
<thead>
<tr>
<th>Fat soluble vitamins</th>
<th>CF patients needing supplements</th>
<th>Starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>PI, northern countries</td>
<td>400–10 000 IU/day</td>
</tr>
<tr>
<td>D</td>
<td>PI, Schilling test &lt;45% after ileal resection</td>
<td>100–400 IU/day, depending on serum level</td>
</tr>
<tr>
<td>E</td>
<td>All</td>
<td>100–400 IU/day</td>
</tr>
<tr>
<td>K</td>
<td>Schilling test &lt;45% after ileal resection</td>
<td>1 mg/day–0.1 mg/week</td>
</tr>
<tr>
<td>B12</td>
<td>Schilling test &lt;45% after ileal resection</td>
<td>100 μg i.m./month</td>
</tr>
<tr>
<td>Other water-soluble</td>
<td>None if dietary intake is normal</td>
<td></td>
</tr>
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PI, pancreatic insufficient.
range 18–55) clearly showed that exercise capacity assessed by measurement of VO$_{2\text{max}}$ and nutritional status assessed by BMI were very good predictors of bone mineralization.$^{70}$

β-carotene supplementation remains controversial. A daily dose of 0.5–1 mg/kg may be necessary in case of low plasma β-carotene levels. Since plasma β-carotene concentrations above normal values have been associated with a higher incidence of lung cancer in smokers (with high oxidative stress) monitoring of blood levels may be mandatory.

Although there is growing evidence that vitamin K deficiency plays an important role in the osteoporosis of CF, the use and dosage of vitamin K supplementation remains unclear, but recent work supports the routine prescription of vitamin K supplements inpatients with pancreatic insufficiency.$^{71}$

There is no indication for routine supplements of water-soluble vitamins, except in the case of patients who have had ileal resection and are, therefore, at risk of vitamin B$_{12}$ deficiency.

**MINERALS**

Because of the increased loss of sodium and chloride in sweat, daily supplementation of salt on an individual basis should be given during fever, vigorous exercise or high environmental temperature. Supplementation of iron, zinc or selenium is only necessary when there is biochemical evidence of deficiency.

**CONCLUSIONS**

Maintenance of a normal nutritional status is an important task for the multidisciplinary team managing patients with CF. It is made more difficult with increasing age, chronic colonisation with *Pseudomonas aeruginosa* and the onset of progressive respiratory failure.

A stepwise management programme is necessary, starting with boosted oral nutrition and progressing as necessary to oral supplementation, enteral nutrition and, rarely parenteral nutrition. The amount and type of caloric supplementation has to be tailored to the individual patient.

**Practice points**

- regular dietetic surveillance is essential, problems should be anticipated
- most patients need PERT but pancreatic insufficiency should first be demonstrated
- caloric (energy) needs are frequently increased, but appetite may be poor
- supplements are most effective when given at earliest evidence of nutritional decline
- simple supplements are usually as effective as more expensive options
- vitamin and mineral deficiencies may be subclinical, monitoring should be biochemical
- CF-related diabetes usually needs insulin
REFERENCES

1. Dodge JA & Lewis PA. Cystic fibrosis is no longer an important cause of childhood death in the UK. Arch Dis Child 2005; 90: 547.


Research Agenda

- more efficient enzyme substitutes are needed
- why does CF-related diabetes adversely affect lung function?
- the pathogenesis of osteopenia needs elucidation
- can antioxidant mechanisms be improved? What is the role of β-carotene?
- is essential fatty acid imbalance a primary feature of CF?
- is there a role for n3 fatty acid supplements?


FURTHER READING

2. Sinaasappel M, Stern M, Littlewood JM et al., 2002 (Ref. 6).
6. Aris RM, Merkel PA, Bachrach LK et al., 2005 (Ref. 60).